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FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 07/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/977,221	MORTEN, JOHN EDWARD NORRIS	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-6 and 8-30* is/are pending in the application.

4a) Of the above claim(s) *2-6,8-13 and 28-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4/21/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group III in the paper filed on 5/21/03 is acknowledged. In response to a further election requirement to select a single group of polymorphisms for examination, applicant selected a group containing a single polymorphism, that is the polymorphism disclosed at position 1513 of SEQ ID NO: 2.

2. The traversal is on the ground(s) that each of the claimed nucleotide polymorphisms is in the same gene and thus it would not require undue burden to search the art for each individual polymorphism. This is not found persuasive because the individual search and examination of 43 different polymorphisms, even within the same gene poses a substantial burden on the examiner. Polymorphisms are not reported in the literature in any art recognized standard format, and the determination of whether or not a given reference teaches a give polymorphism requires separate analysis of each reference. Further, methods for detecting each polymorphism must be given separate consideration under each of the statues. Finally, applicant asserts that because all of the SNP's are within the same gene they should be examined together because they all encode a human P2X7 protein. This is not persuasive because even though all of the single nucleotide polymorphisms are within the same gene, they each would assert their own effect on the activity of the P2X7 nucleic acid sequence which they are contained within, they each have distinct potential prognostic and/or diagnostic effects, and many of them lead to changes in the coding sequence which will lead to the production of proteins whose functionality is unknown. The requirement is still deemed proper and is therefore made FINAL. gd.

3. The amendment filed on 5/21/03 has been entered. Claims 1 and 7 were cancelled and claims 14-30 have been added. Claims 2-6 and 8-13 are withdrawn from prosecution. In addition, new claims 28-30 are withdrawn from prosecution as being drawn to a method for detecting a non-elected combination of polymorphisms. Claims 14-27 are examined herein.

Priority

4. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 14-27 of this application. The instant specification provides support under 35 U.S.C. 112 for claims 14-27 insofar as the specification teaches that the polymorphism at nucleotide 1513 of SEQ ID NO: 2 causes loss of function in $P2X_7$ (p. 21, lines 4-5), a receptor which is a ligand-gated cation-selective channel that mediates ATP-induced apoptosis of cells. However, neither the provisional application does not provide adequate support for the claimed invention under 112 1st paragraph, nor do either of the foreign priority documents (see rejections herein under 112 1st paragraph and 101). Therefore, the filing date of the instant application is considered to be the instant filing date, or 10/16/2001. It is of interest to note that the fact that the polymorphism at position 1513 of SEQ ID NO: 2 causes loss of function of $P2X_7$ is first disclosed in foreign priority document filed 4/6/01.

Specification

6. The disclosure is objected to because of the following informalities: The information in the table on pages 17-19 is misaligned. The spacing between the lines in the "polymorphism" column is not the same as the spacing between the lines of the "protein change" and "frequency" columns, so as one reads across a line it is difficult to determine which information corresponds

with which polymorphism. For example, if one reads across the line which teaches the 1513 A→C polymorphism, it appears that the table is teaching that this is a "silent" polymorphism because the word "silent" appears to be directly next to the 1513 A→C line. However, if one counts down from the first polymorphism in exon 13 the 1513 polymorphism is the fifth listed, and if one counts to the fifth description in the "protein change" column, one finds that the fifth entry is "glu496ala." The misalignment of the columns makes the table very difficult to interpret.

Appropriate correction is required.

7. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed, for example "Detection of polymorphisms in the human $P2X_7$ gene."

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 14-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14-24 are is indefinite because the preamble of the claim recites a method for determining the presence or absence of a single nucleotide polymorphism, but the method steps of the claims do not clearly set forth that this recited goal is accomplished. For example, claim 14 recites a final process step requiring a step of testing the sample to determine the identity of the nucleotide. The claims do not clarify how the testing step which results in determining the

identity of the nucleotide results in determining the presence or absence of a single nucleotide polymorphism. That is, it is unclear how one practicing the invention knows from the testing step whether one has in fact determined the presence or absence of a single nucleotide polymorphism.

Claim 14 is further indefinite because it is unclear what is meant by a position "corresponding" to position 1513 of SEQ ID NO: 2. That is, is applicant referring to position 1513 of SEQ ID NO: 2 or are other positions within SEQ ID NO: 2 within the scope of this recitation? To have a position "corresponding" to position 1513 of SEQ ID NO: 2, does a nucleic acid simply have to have 1513 nucleotides or is some other structural limitation implied by the use of this language? Claims which depend from claim 14 are indefinite over this recitation as well. Claims 18 and 19 are further indefinite because they refer to "the nucleotide at position 1513 of SEQ ID NO: 2" but the claim from which they depend does not specifically refer to a particular nucleotide at position 1513 but instead refer to a nucleotide at a position corresponding to position 1513 of SEQ ID NO: 2.

Claim 20 is also indefinite because it is unclear what is meant by a position "corresponding" to position 1513 of SEQ ID NO: 2. That is, is applicant referring to position 1513 of SEQ ID NO: 2 or are other positions within SEQ ID NO: 2 within the scope of this recitation? To have a position "corresponding" to position 1513 of SEQ ID NO: 2, does a nucleic acid simply have to have 1513 nucleotides or is some other structural limitation implied by the use of this language? Claim 21, which depends from claim 20 is indefinite over this recitation as well.

Claims 22, 23, 24, 25, 26, and 27 are also indefinite because it is unclear what is meant by a position "corresponding" to position 1513 of SEQ ID NO: 2. That is, is applicant referring to position 1513 of SEQ ID NO: 2 or are other positions within SEQ ID NO: 2 within the scope of this recitation? To have a position "corresponding" to position 1513 of SEQ ID NO: 2, does a nucleic acid simply have to have 1513 nucleotides or is some other structural limitation implied by the use of this language?

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 19, 24, and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

With regard to claims 19 and 24, the new limitation of "determining that the nucleotide at position 1513 of SEQ ID NO: 2 is not an A" in claim 19 and "determining that the nucleotide in the sample corresponding to position 1513 of SEQ ID NO: 2 is not an A" in claim 24 appear to represent new matter. In applicant's remarks filed with the amendment, applicant asserts that

support for claims 19 and 24 can be found on page 3, line 31; in the table on page 18; and on page 20 in the first table. These each provide basis for a limitation wherein the nucleotide at position 1513 of SEQ ID NO: 2 is an A or a C, however none of them provide specific basis for the limitation that the nucleotide is "not an A." First, it is noted that line 3 of page 31 does not discuss a polymorphism at position 1513 of SEQ ID NO: 2, but instead a polymorphism at position 1315 of SEQ ID NO: 2. It assumed that applicant meant to point to line 1 of page 4 which teaches that the polymorphism at position 1513 "is presence or an A and/or C." At page 18 the table recites "1513 A→C." At page 20, the first table shows that the position 1513 can be an A or a C. Specifically, the exclusionary proviso in which the nucleotide is "not an A" is not found in the specification. As noted by MPEP 2173.05(i),

> "Any negative limitation or exclusionary proviso must have basis in the original disclosure. See Ex parte Grasselli , 231 USPQ 393 (Bd. App. 1983) aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement."

Since no explicit basis has been identified for the newly added negative limitation, claims 19 and 24 are rejected as incorporating new matter.

With regard to claim 27, the newly added method step which recites a frequency from a population "at large" is also new matter. The remarks filed with the amendment point to basis for this claim at pages 11-12, lines 24-3; and in the first table on page 20. Pages 11-12 teach that the polymorphism can be used as genetic markers in linkage studies, and discuss determining haplotypes in a "population of interest" but do not describe or define a "population at large." Thus, claim 27 is rejected as incorporating new matter in view of the addition of this limitation to the claim.

12. Claims 14-19, 25, and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the Invention and Breadth of the Claims

The claims are all drawn to methods of detecting a single nucleotide polymorphism within the human P2X7 gene. The particular polymorphism is an A→C transition at position 1513 of SEQ ID NO: 2. Rejected claims 14-19 and 25 require that the nucleic acid sample assayed be obtained from an individual identified as having or at risk of having a "P2X7 mediated disease." Rejected claim 27 requires that the nucleic acid sample be obtained from a person having or at risk of having a "P2X7 mediated disease." Thus, the nature of the claimed invention requires knowledge of the identity of diseases which are in fact mediated by P2X7.

State of the Art

The prior art teaches the nucleic acid sequence of the genomic and cDNA of the human P2X7 receptor, and that this receptor is a ligand-gated channel whose activation leads to an inward ionic current and cell permeabilization (see Buell *et al.* (1998) and Rassendren *et al.* (1997) and US 6133434, for example). Gu *et al.* further teach that this receptor is a ligand-gated chation channel that has been shown to mediate the ATP-induced apoptotic death of monocytes, macrophages, and lymphocytes (p. 3), and Gu *et al.* teach a single nucleotide polymorphism that is an A→C transition at position 1513. Gu *et al.* further teach that this polymorphism causes loss of function of the P2X7 polypeptide.

The prior art does not teach that any particular diseases are mediated by P2X7. In fact, Gu *et al.* identify the loss of function polypeptide to be present in 10 out of 45 normal, healthy subjects, demonstrating that even with loss of P2X7 patients remain healthy.

Baxter *et al.* (WO 99/29661) teach compositions that are effective as P2X7 antagonists, and teach that P2X7 "may" play a role in inflammatory, immune or cardiovascular diseases, but Baxter *et al.* do not teach that any of these diseases are mediated by P2X7. Their statement is a statement is essentially a prophetic statement that these types of diseases could be associated with P2X7, but they do not provide any evidence to support this assertion.

Direction Provided and Working Examples

The specification also teaches a single nucleotide polymorphism that is an A→C transition at position 1513 of SEQ ID NO: 2. The specification, at page 21 cites Gu *et al.* as teaching that this polymorphism causes loss of function of P2X7.

The specification further asserts that compounds acting on P2X7 are "indicated" as pharmaceuticals for a wide variety of conditions, including rheumatoid arthritis, diabetes, Alzheimer's disease, stroke, varicose veins, and some cancers (p. 1). The specification does not provide any further guidance as to whether these diseases are in fact mediated by P2X7, or how to identify a risk of having such diseases. The specification does not provide any working examples of methods for identifying patients as having or at risk of having P2X7 mediated diseases. Furthermore, the specification does not disclose any relationship between P2X7 mediated diseases and the polymorphism at position 1513 of SEQ ID NO: 2. While the specification does refer generically to "P2X7 mediated" diseases, the specification does not particularly define what is required for a disease to be mediated by P2X7.

Level of Skill and Level of Unpredictability

The level of skill in the art is quite high, but the unpredictability in the art is higher. There is no way of predicting which diseases, of the variety of possibilities proposed in the specification, are in fact "P2X7 mediated." This is especially pointed out by the fact that Gu *et al.* observed that nearly a quarter of normal, healthy patients have at least one copy of the P2X7 gene which encodes a receptor with loss of function. Furthermore, in the post filing date art Dasgupta *et al.* were unable to identify an association between P2X7 polymorphisms and risk of chronic lymphocytic leukemia or with response to treatment, when trying to confirm previously demonstrated relationships. Thus, even when a relationship between the polymorphism and a disease state or response to treatment is noted in an isolated population, it is still unpredictable as to whether this indicates that the disease is mediated by the P2X7 gene or if it is merely a marker for the disease state.

Quantity of Experimentation

Absent any specific guidance from the specification or the prior art, in order to practice the claimed invention, one would have to undertake extensive studies to confirm the fact that the any particular disease, let alone all of the diseases recited in claim 22, is in fact a "P2X7 mediated disease." One would have to undertake extensive biochemical analysis of patients who have the diseases in order to determine the etiology of the disease and the role of the P2X7 cation channel in the diseases.

Conclusion

Thus, in light of the nature of the invention, the scope of the claims, the lack of working examples, the lack of teaching in the prior art, the high level of unpredictability and the high

level of experimentation necessary to determine which diseases are in fact "P2X7 mediated diseases," it is concluded that it would require undue experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 101

13. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

14. Claims 14-27 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 14-24 are drawn to methods for determining the presence a polymorphism at position 1513 of SEQ ID NO: 2. Claims 25-26 recite methods of characterizing the genotype of a human and include a step of determining the identity of a nucleotide at position 1513 of instant SEQ ID NO: 2. Claim 27 recites a method of performing a linkage study wherein the identity of a nucleotide at position 1513 is determined for at least two individuals having or at risk for having a P2X7 mediated disease, and correlating the frequency of a "C" at position 1513 with the frequency with which C occurs in the "population at large." Instant SEQ ID NO: 2 encodes the human P2X7 gene, a receptor which is a ligand-gated cation-selective channel that mediates ATP-induced apoptosis of cells. The polymorphism being detected is an A→C transition which results in an amino acid change at position 496 of the encoded polypeptide and the encoded polypeptide exhibits loss of function when the "C" allele is present. There is no well established utility for the claimed invention.

The specification asserts that the "knowledge of polymorphisms can be used to help identify patients most suited to therapy with particular pharmaceutical agents (p. 2)," but the

specification does not provide any evidence that the polymorphism at position 1513 of SEQ ID NO: 2 is in fact correlated with patient response to any particular pharmaceutical agent. The specification asserts at page 3 that humans may be tested for predisposition or susceptibility for disease (lines 6-7), but the specification does not provide any evidence that the polymorphism is associated with any particular human disease. The specification asserts that the claimed methods can be used in the development of new drug therapies stating that "Identification of a link between a particular allelic variant and predisposition to disease development or response to drug therapy may have a significant impact on the design of new drugs (p. 7)" but again, the specification fails to provide of a link between a particular allelic variant and predisposition to disease development or response to drug therapy. The specification asserts that the polymorphisms can be used in genetic markers in linkage studies, and in fact the method of claim 27 sets forth such a method of study. None of these asserted utilities are specific to the methods claimed herein, because any method of detecting a polymorphism in a gene can be used to determine if any of these relationships exist between the polymorphism and putative related diseases. Any polymorphism can generically be asserted as being useful in a linkage study. None of these asserted utilities are substantial in view of the claimed methods because they all require further experimentation to reasonably confirm that such a utility exists. The asserted utilities for methods of the claimed invention are an invitation to the practitioner to determine if in fact a specific and substantial utility exists for the disclosed invention.

Claims 14-27 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a

well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

For all the above reasons, the disclosure is insufficient to teach one of skill in the art how to use the invention. A review of *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) clearly points out the factors to be considered in determining whether a disclosure would require undue experimentation and include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. All of these factors are considerations when determining the whether undue experimentation would be required to use the claimed invention.

The **nature of the invention and the breadth of the claims** are discussed in the 101 rejection.

State of the Art

The prior art teaches the nucleic acid sequence of the genomic and cDNA of the human P2X7 receptor, and that this receptor is a ligand-gated channel whose activation leads to an inward ionic current and cell permeabilization (see Buell *et al.* (1998) and Rassendren *et al.* (1997) and US 6133434, for example). Gu *et al.* further teach that this receptor is a ligand-gated chation channel that has been shown to mediate the ATP-induced apoptotic death of monocytes, macrophages, and lymphocytes (p. 3), and Gu *et al.* teach a single nucleotide polymorphism that is an A→C transition at position 1513. Gu *et al.* further teach that this polymorphism causes loss of function of the P2X7 polypeptide.

The prior art does not teach that any particular diseases are mediated by P2X7. In fact, Gu *et al.* identify the loss of function polypeptide to be present in 10 out of 45 normal, healthy subjects, demonstrating that even with loss of P2X7 patients remain healthy.

Baxter *et al.* (WO 99/29661) teach compositions that are effective as P2X7 antagonists, and teach that P2X7 "may" play a role in inflammatory, immune or cardiovascular diseases, but Baxter *et al.* do not teach that any of these diseases are mediated by P2X7, merely that they might play a role in disease. Their assertion is prophetic.

Direction Provided and Working Examples

The specification also teaches a single nucleotide polymorphism that is an A→C transition at position 1513 of SEQ ID NO: 2. The specification, at page 21 cites Gu *et al.* as teaching that this polymorphism causes loss of function of P2X7.

The specification further asserts that compounds acting on P2X7 are "indicated" as pharmaceuticals for a wide variety of conditions, including rheumatoid arthritis, diabetes, Alzheimer's disease, stroke, varicose veins, and some cancers (p. 1). The specification does not provide any further guidance as to whether these diseases are in fact mediated by P2X7, or how to identify a risk of having such diseases. The specification does not provide any working examples of methods for identifying patients as having or at risk of having P2X7 mediated diseases. Furthermore, the specification does not disclose any relationship between P2X7 mediated diseases and the polymorphism at position 1513 of SEQ ID NO: 2. Based on the teachings of the specification, one would not know how to use the claimed invention because one does not know the relevance of detecting the recited mutation.

The amount of direction or guidance presented in the specification with regard to how to use the instant invention is minimal. That is, the specification does not provide any guidance as to how the polymorphism at position 1513 of SEQ ID NO: 2 would be associated with any pharmaceutical agent. The specification does not discuss whether this particular polymorphism will increase the likelihood of a positive or negative response to any drug. The specification provides no guidance or working examples that teach or demonstrate the ability to use the disclosed polymorphic site as a marker for any disease in particular, or for disease in general, or how to use the disclosed polymorphism to select a proper course of treatment of a disease.

Level of Skill in the art, Level of Unpredictability, and Quantity of Experimentation

The level of skill in the art is quite high, but the unpredictability in the art is higher. There is no way of predicting which diseases, of the variety of possibilities proposed in the specification, are in fact "P2X7 mediated." This is especially pointed out by the fact that Gu *et al.* observed that nearly a quarter of normal, healthy patients have at least one copy of the P2X7 gene which encodes a receptor with loss of function.

There is also a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627).

Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

The significance of the instantly disclosed P2X7 polymorphism remains highly unpredictable, as the instant specification and the prior art both demonstrate that healthy subjects carry this polymorphism. Thus determining how to use the claimed methods as asserted by applicant, requires the knowledge of unpredictable and potentially non-existent associations between the polymorphism and some disease or disease state. Even if the elected polymorphism is in some way associated with some disease, it is difficult (if not impossible) to know or predict from the teachings of the specification which disease or how the polymorphism is associated. That is, it is unpredictable as to whether the presence of a particular allele the polymorphism would confer a higher or lower likelihood of having the disease. In this case, the possible uses

for the claimed methods are undefined, beyond the suggestion that they can be used to detect a disease associated with the P2X7 gene prior to treatment with a P2X7 drug.

Furthermore, in the post filing date art Dasgupta *et al.* were unable to identify an association between the polymorphism at 1513 of P2X7 and risk of chronic lymphocytic leukemia or with response to treatment, when trying to confirm previously demonstrated relationships. Thus, even when a relationship between the polymorphism and a disease state or response to treatment is noted in an isolated population, it is still unpredictable as to whether this indicates that the disease is mediated by the P2X7 gene or if it is merely a marker for the disease state. Li *et al.* were unable to detect a relationship between the 1513 polymorphism and tuberculosis, but were able to demonstrate an association between a promoter polymorphism and the protection against the disease. Thus, even within the P2X7 gene, Li *et al.* demonstrate that it is highly unpredictable as to whether or not a particular polymorphism will be associated with a phenotype, and even if one polymorphism in a gene is associated with the phenotype, a different polymorphism may not be.

The quantity of experimentation required to discover how to use the instant invention is very high. In order to use the claimed invention as asserted by the specification, one would have to establish a relationship between the polymorphism at nucleotide 1513 of SEQ ID NO: 2 some disease state or some disease treatment method. Indeed, even to use the method of claim 1 to identify patients suited for particular pharmaceutical agents, one would need to know that the polymorphism at nucleotide 1513 of SEQ ID NO: 2 was in some way associated with response to some pharmaceutical agent. In order to obtain the type of information necessary to practice the claimed invention, one would be required to undertake the screening of hundreds or

thousands of patients as well as possible hundreds of diseases or pharmaceutical agents. Even if such experiments were undertaken, it would still be unpredictable as to whether any associations would be detected, in light of the unpredictability of such associations, as already discussed. Thus, while one could perform further research to determine whether applicant's method would be useful in disease detection and/or treatment, it is unknown as to what the outcome of such research might be and as to whether any quantity of experimentation would result in the identification of an association between the P2X7 1513 polymorphism and any disease or condition. Likewise, with respect to claim 27, it is be unpredictable as to whether the instant polymorphism is in fact linked to any disease state or treatment response. Further, absent a teaching the polymorphism at position 1513 of SEQ ID NO: 2 is not associated with such conditions, it is further unpredictable as to whether detection of the polymorphism would be useful in predicting, e.g., the absence or decreased likelihood of such conditions.

Conclusion

Thus, in light of the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of direction or working examples in the specification, and the high quantity of experimentation that would be required to practice the claimed invention, it is concluded that undue experimentation would be required to use the instantly claimed invention. Thus, although the specification certainly enables one to detect the presence of the polymorphism(s) (i.e. the "make" portion of 112 1st paragraph), it would require undue experimentation in order to determine how to use the claimed invention.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

16. Claims 14-16, 18-19, and 23-27 are rejected under 35 U.S.C. 102(a) as being anticipated by Gu *et al.* (JBC Papers in Press. Published on January 9, 2001 as Manuscript M010353200).

Gu *et al.* teach a method for determining the presence or absence of a single nucleotide polymorphism (SNP) in a $P2X_7$ gene, the method comprising:

(a) providing a nucleic acid from a human identified as having or at risk for having a P2X7 mediated disease, wherein the sample comprises a nucleotide at a position corresponding to position 1513 of SEQ ID NO: 2; and

(b) testing to determine the identity of the nucleotide.

Specifically, Gu *et al.* teach methods in which DNA samples in the form of human leucocytes were obtained from 45 normal subjects and one patient with B-chronic lymphocytic leukemia (p. 6). The patient with B-chronic lymphocytic leukemia is considered to be a patient identified as having a P2X7 mediated disease because, as recited in claim 16, such diseases include growth and metastases of malignant cells, which the patient with B-chronic lymphocytic leukemia has. However, Gu *et al.* do not specifically teach that this disease is a "P2X7 mediated disease," but it is considered to be within this group for the purposes of evaluating the prior art in light of Applicant's disclosure. Gu *et al.* utilize DNA sequencing of PCR products (p. 6) to

identify a single nucleotide polymorphism in the C-terminal tail of the P2X7 gene, specifically teaching the at the polymorphism is an A to C substitution at position 1513 (p. 9).

With regard to claim 15, the nucleic acid sample inherently comprises a fragment of P2X7 DNA because they isolate whole genomic DNA from the sample, further, Gu *et al.* specifically amplify a portion of the P2X7 gene for analysis (p. 7).

With regard to claim 16, as previously noted, Gu *et al.* test for a patient with a polymorphism having or at risk of having growth and metastases of malignant cells.

With regard to claims 18 and 19, Gu *et al.* determine that the nucleotide at position 1513 is a C, and not an A in one of three patients with malignant B-lymphocytes (p. 13).

With regard to claims 23 and 24, Gu *et al.* teach a method for determining the presence or absence of a SNP in a P2X7 gene in a nucleic acid sample of a human, the method comprising determining that the nucleotide in the sample corresponding to position 1513 of SEQ ID NO: 2 is a C, and not an A (p. 9).

With regard to claims 25 and 26, Gu *et al.* teach a method for characterizing the genotype of a human diagnosed as having or being at risk for having a P2X7 mediated disease (i.e. growth and metastases of malignant cells), the method comprising

(a) providing a nucleic acid from a human identified as having or at risk for having a P2X7 mediated disease, wherein the sample comprises a nucleotide at a position corresponding to position 1513 of SEQ ID NO: 2; and

(b) testing to determine the identity of the nucleotide and

(c) recording the identity of the nucleotide in a print or computer readable medium. Steps (a) and (b) are previously discussed. With regard to step (c) Gu *et al.* at the very least recorded the identity of the nucleotide in their manuscript.

With regard to claim 27, Gu *et al.* teach a method of performing a linkage study, the method comprising,

(a) providing a nucleic acid sample from each of two or more individuals having or at risk of having a P2X7 mediated disease, wherein the sample comprises a nucleotide at a position corresponding to position 1513 of SEQ ID NO: 2;

(b) testing each sample to determine the identity of the nucleotide; and

(c) correlating (i) the frequency with which a C occurs at the position corresponding to position 1513 of SEQ ID NO: 2 in the samples, with (ii) the frequency with which C occurs at the psitoion corresponding to postion 1513 of SEQ ID NO: 2 in nucleic acid samples from the population at large.

With regard to step (a), Gu *et al.* teach providing nucleic acid samples from 45 humans, and testing for the identity of nucleotide corresponding to 1513 of SEQ ID NO: 2. These individuals are considered to be "at risk of having" a P2X7 mediated disease, because, it is with the broadest reasonable interpretation to conclude that all humans are at risk of having any number of the diseases considered to be "P2X7 mediated" by applicant. All humans are at risk, to some degree, of having P2X7 mediated diseases. Neither the specification nor the claims provide a definition of the level of risk required for an individual to be "at risk" and thus, the claims encompass even individuals at a very low risk of obtaining any P2X7 mediated disease. Thus, the humans taught by Gu *et al.*

Further, with regard to step (c), Gu *et al.* correlate the frequency of the mutant allele (the C) in the population they sampled with the frequency with which "C" occurs in the entire Caucasian population when they conclude that based on the frequency of the mutant allele within the population they studied the A→C base change in the P2X7 gene meets the criteria for a single nucleotide polymorphism (p. 9).

Thus, the teachings of Gu *et al.* meet the limitations of all of the rejected claims.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 17 and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al. in view of Newton *et al.* (Nucleic Acids Research (1989 April 11) 17(7)2503-2516).

With regard to claim 17, Gu *et al.* teach a method for determining the presence or absence of a single nucleotide polymorphism (SNP) in a $P2X_7$ gene, the method comprising:

(a) providing a nucleic acid from a human identified as having or at risk for having a P2X7 mediated disease, wherein the sample comprises a nucleotide at a position corresponding to position 1513 of SEQ ID NO: 2; and

(b) testing to determine the identity of the nucleotide.

Specifically, Gu *et al.* teach methods in which DNA samples in the form of human leucocytes were obtained from 45 normal subjects and one patient with B-chronic lymphocytic leukemia (p. 6). The patient with B-chronic lymphocytic leukemia is considered to be a patient

identified as having a P2X7 mediated disease because, as recited in claim 16, such diseases include growth and metastases of malignant cells, which the patient with B-chronic lymphocytic leukemia has. Gu *et al.* utilize DNA sequencing of PCR products (p. 6) to identify a single nucleotide polymorphism in the C-terminal tail of the P2X7 gene, specifically teaching the at the polymorphism is an A to C substitution at position 1513 (p. 9).

With regard to claims 20 and 21, Gu *et al.* teach a method for determining the presence or absence of a SNP in a P2X7 gene comprising:

(a) providing a nucleic acid sample from a human, wherein the sample comprises a nucleotide at a position corresponding to position 1513 of SEQ ID NO: 2 (p. 6). The nucleic acid sample inherently comprises a fragment of P2X7 DNA because they isolate whole genomic DNA from the sample, further, Gu *et al.* specifically amplify a portion of the P2X7 gene for analysis (p. 7).

With regard to claim 22, Gu *et al.* teach a method for determining the presence or absence of a SNP in a P2X7 gene, the method comprising:

(a) providing a nucleic acid sample from a human identified as having, or at risk of having growth and metastases of malignant cells (p. 6);

Gu *et al.* further teach determining the identity of the nucleotide at a position corresponding to position 1513 of SEQ ID NO: 2 via sequencing of PCR fragments (p. 7), but Gu *et al.* do not teach methods which use any of the techniques particularly recited in the rejected claims, for example ARMS™.

However, at the time the invention was made there were a multiplicity of different methods for detection of single nucleotide polymorphisms, as are discussed in the specification

at page 6. For example, Newton *et al.* teach a method for detecting single base changes that allows genotyping solely by inspection of reaction mixtures after electrophoresis. They call the method ARMS™. (See abstract and throughout).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the polymorphism detection method taught by Gu *et al.* so as to have detected the polymorphism using the ARMS™ method taught by Newton *et al.* One would have been motivated to make such a substitution because Newton *et al.* teach many advantages of using the ARMS™ system, including that it is a simple and reliable and does not require a host of time consuming steps, such as sequence analysis of PCR products. Thus, in light of the teachings of Gu *et al.* in view of Newton *et al.* the claims are prima facie obvious.

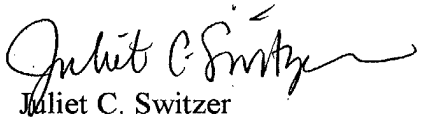
Conclusion

19. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Juliet C. Switzer
Examiner
Art Unit 1634

July 25, 2003